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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,060	07/10/2000	Neil Andrew Williams	CTH-03	6761

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ST. ONGE STEWARD JOHNSTON & REENS LLC
986 Bedford Street
Stamford, CT 06905-5619

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,060	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *101-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *101-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 101-114 are pending.

2. In view of the amendment filed 6/23/05, the following rejection remains.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 101-114 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims encompass a method of treating any subject for IgE mediated Type I allergies such as asthma, allergic cough, allergic rhinitis, conjunctivitis, atopic eczema, dermatitis, uticaria, hives comprising administering to the subject a therapeutically effective amount of an agent such as Etx, Ctx, EtxB and EtxB that binds to GM1 and coadministered with any allergen that is not coupled.

The specification discloses a method for screening agents capable of modulating ganglioside associated activity. The specification further discloses the use of GM1 binding agent such as Ctx, Etx, CtxB and EtxB in the manufacture of a medicament to affect an allergic condition and/or a hypersensitivity condition wherein the EtxB agent is not coupled to an antigen/allergen (page 28, line 26-30, page 29). The specification asserts that EtxB is effective for treating allergy by blocking an IgE mediated response through modulation of a ganglioside associated activity. The specification defines mucosal surfaces includes but is not limited to oral, sublingual, intranasal, vaginal, rectal, salivary, intestinal and conjunctival surfaces.

However, the specification does not teach the "effective amount" of Ctx, Etx, CtxB and EtxB to be coadministered with the allergen/antigen. The specification does not teach the route of administration i.e. mucosal, intravenous, intramuscular, or subcutaneous that is effective for the claimed method. This is because immunomodulation by Ctx, Etx, CtxB and EtxB depends on the route of administration and the structure of the allergen.

Wiedermann *et al,* of record, teach suppressive versus stimulatory effects of allergen/cholera toxoid (CtB) conjugates depending on the nature of the allergen in which murine model of type I allergy as well as the route of administration (See abstract, in particular). In particular, cholera toxin when administered simultaneously with an antigen by the mucosal route, it enhances immune response to the co-administered antigen (see page 1132, col. 1 first paragraph, in particular). In contrast, mucosal administration of B subunit of cholera toxin (CTB) physically coupled to an antigen enhances peripheral tolerance induction (see page 1132, col. 1, first paragraph, in particular).

Kagan *et al*, of record, teach presently, the only available treatment of food allergies is dietary vigilance and administration of self-injectable epinephrine (abstract, in particular).

Given the unlimited number of allergen and lack of in vivo working example, it is unpredictable which method is efficacious for treating a subject with asthma, allergic rhinitis, atopic eczema, dermatitis or hives.

Herz *et al*, of record, teach allergens can differ in their immunogenicity as well as in their capacity to act as tolerogens (See abstract, page 274, nature of the antigen, in particular). Herz *et al* teach until now no mouse model has been available which resembles all of human bronchial asthma (page 272, column 2, Animal models of type I allergy and asthma, in particular). Each individual mouse strain demonstrates a unique response pattern following immunization of allergens. The same allergen causes different phenotype dependent on genetical prerequisites (page 273, column 1, in particular). Further, the route of allergen administration has important impact on the quality of the immune response (See page 273, column 2, in particular). Herz et al teach that dependence of experimental model and the antigen used, the effects as well as the mechanisms of action can vary which might indicate the complexity of predicting clinical consequences of any therapeutic approach (see page 279, in particular).

Tamura et al, of record, teach that the *physical association* of LTB and antigen such as OVA is required to mediate immune suppression (See page 228, column 1, Figure 2, in particular).

Hoynes et al teach that allergic sensitization is a Th2 process where Th2 T helper cells are more efficient in secreting IL-4, IL-5, and IL6 which promote the growth and differentiation of B cells and induce isotype class switching toward IgG1 and IgE in human (see page 180, col. 1, in particular). Hoynes et al teach successful treatment of allergy is accompanied by a *decrease*

in Th2-type cytokine production and a concomitant switch to Th1 immune response (see page 180, col. 2, in particular).

Williams et al teach that co-administering ExtB agent that binds to GM1 not couple to antigen such as collagen type II (CII) to DBA mice *increases* IL-4 (Th2 immune response) with a concomitant reduction in interferon gamma (Th1 immune response) (see abstract, page 5291, Materials and methods, col. 2, first paragraph, in particular). Since allergic conditions and co-administering EtxB agent with an antigen are known in the art to promote Th2 response, it is not clear the claimed method is effective for treating any type I allergy that are IgE mediated using EtxB in the absent of in vivo working example.

For these reasons, it would require undue experimentation of even one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed and declaration by Neil Williams filed 12/20/02 have been fully considered but are not found persuasive.

Applicants' position is that claim 101 sets forth in independent form the exact claim which the Examiner stated was acceptable in the Office Action mailed May 13, 2004, page 4, Paragraph 4.

It appears that applicant's response addressed the office action that were mailed May 13, 2004, and not the non-final Office action that was subsequently mailed in Dec 30, 2004. In response to applicant's argument that the new claims are enabled based on the retracted Office Action, an examiner is not prohibited from making a new grounds of rejection provided it is warranted during the prosecution of a patent application. In the Office Action that was mailed Dec 30, 2004, none of the claims appear to be enabled. This is because of the following reasons: (1) the lack of guidance as to the effective amount of Etx, Ctx, EtxB and CtxB that bind to GM1 to be co-administered with which allergen. (2) the lack of guidance as to the route of administration (3) the nature of the allergen and (4) the subject population.

As evidence by the references cited, Wiedermann *et al,* of record, teach suppressive versus stimulatory effects of allergen/cholera toxoid (CtB) conjugates depending on the nature of the allergen in which murine model of type I allergy as well as the route of administration (See abstract, in particular). In particular, cholera toxin when administered simultaneously with an antigen by the mucosal route, it enhances immune response to the co-administered antigen (see page 1132, col. 1 first paragraph, in particular). In contrast, mucosal administration of B subunit of cholera toxin (CTB) physically coupled to an antigen enhances peripheral tolerance induction (see page 1132, col. 1, first paragraph, in particular).

Kagan *et al*, of record, teach presently, the only available treatment of food allergies is dietary vigilance and administration of self-injectable epinephrine (abstract, in particular).

Given the unlimited number of allergen and lack of in vivo working example, it is unpredictable which method is efficacious for treating a subject with asthma, allergic rhinitis, atopic eczema, dermatitis or hives.

Herz *et al*, of record, teach allergens can differ in their immunogenicity as well as in their capacity to act as tolerogens (See abstract, page 274, nature of the antigen, in particular). Herz *et al* teach until now no mouse model has been available which resembles all of human bronchial asthma (page 272, column 2, Animal models of type I allergy and asthma, in particular). Each individual mouse strain demonstrates a unique response pattern following immunization of allergens. The same allergen causes different phenotype dependent on genetical prerequisites (page 273, column 1, in particular). Further, the route of allergen administration has important impact on the quality of the immune response (See page 273, column 2, in particular). Herz et al teach that dependence of experimental model and the antigen used, the effects as well as the mechanisms of action can vary which might indicate the complexity of predicting clinical consequences of any therapeutic approach (see page 279, in particular).

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in Th2-type cytokine production and a concomitant switch to Th1 immune response (see page 180, col. 2, in particular).

Williams et al teach that co-administering ExtB agent that binds to GM1 not couple to antigen such as collagen type II (CII) to DBA mice *increases* IL-4 (Th2 immune response) with a concomitant reduction in interferon gamma (Th1 immune response) (see abstract, page 5291, Materials and methods, col. 2, first paragraph, in particular).

For these reasons, it is not clear the claimed method is effective for treating any type I allergy that are IgE mediated using any allergen not coupled to Etx, Ctx, EtxB or CtxB in the absent of in vivo working example.

5. No claim is allowed.

6. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

8. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
September 16, 2005

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600